

**College of Pharmacy**  
**Fourth year. Clinical Pharmacy**  
**Respiratory disorders**  
**Chronic Obstructive Pulmonary Disease**

### **Introduction**

Chronic Obstructive Pulmonary Disease (COPD) is a heterogeneous lung condition characterized by **chronic respiratory symptoms** (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of **the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema)** that cause **persistent, often progressive, airflow obstruction** <sup>(3)</sup>.

It includes **two** principal conditions:

**A-Chronic bronchitis:** Chronic or recurrent **excess mucus secretion with cough** that occurs on most days **for at least 3 months of the year for at least 2 consecutive years**.

**B-Emphysema:** Abnormal, **permanent enlargement of the airspaces** distal to the terminal bronchioles, accompanied by **destruction of their walls, without fibrosis**.

### **Pathophysiology**

1-The **most common cause of COPD is exposure to tobacco smoke**.

2-Inhalation of noxious particles and gases **activates inflammatory cells to release inflammatory mediators**. Inflammatory cells and mediators lead to widespread **destructive changes in airways resulting in chronic airflow limitation**.

3-Chronic hypoxemia and changes in pulmonary vasculature lead to increases in pulmonary pressures. **Sustained elevated pulmonary pressures can lead to right-sided heart failure (cor pulmonale)** characterized by right ventricle hypertrophy in response to increased pulmonary vascular resistance.

### **Clinical presentation**

1-Initial symptoms include **chronic cough and sputum production**; patients may experience cough for several years before dyspnea develops.

2-**Dyspnea** (described by patients as **"increased effort to breathe"** or **"air hunger"**) <sup>(2)</sup> is worse with exercise and **progressive over time**, with decreased exercise tolerance or decline in physical activity. Chest tightness or wheezing may be present.

3-When airflow limitation progresses, patients may have **shallow breathing**, increased **resting respiratory rate**, **"barrel chest"** due to **lung hyperinflation**, **pursed lips during expiration**, use of **accessory respiratory muscles**, and **cyanosis of mucosal membranes**.

### **Diagnosis**

1-Diagnosis is based **on patient symptoms, history** of exposure to risk factors such as tobacco smoke and occupational substances, and **confirmation by pulmonary function testing, such as spirometry (Spirometry assesses lung volumes and capacities**. Forced vital capacity (FVC) is the total volume of air exhaled after maximal inhalation, and **FEV1** is the total volume of air exhaled in 1 second).

2-The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest a four-grade classification of airflow limitation: **mild** (GOLD 1), **moderate** (GOLD 2), severe (GOLD 3), or **very severe** (GOLD 4).

## **Treatment**

**Goals of Treatment:** Prevent or slow disease progression, relieve symptoms, improve exercise tolerance, improve overall health status, prevent and treat exacerbations, prevent and treat complications, and reduce morbidity and mortality (**Further reading 1**).

### **Nonpharmacologic Therapy**

1-**Smoking cessation** is the most important intervention to prevent development and progression of COPD.

2-**Reducing exposure to occupational dust and fumes** as well as other environmental toxins is also important.

3-**Pulmonary rehabilitation programs** include exercise training, breathing exercises, and psychosocial support.

4-Administer the **influenza vaccine annually** during each influenza season. Vaccination against pneumococcal infection is recommended for all adults with COPD.

5-Some patients with severe COPD required **long-term O2 therapy** (by **nasal cannula**).

### **Pharmacologic Therapy**

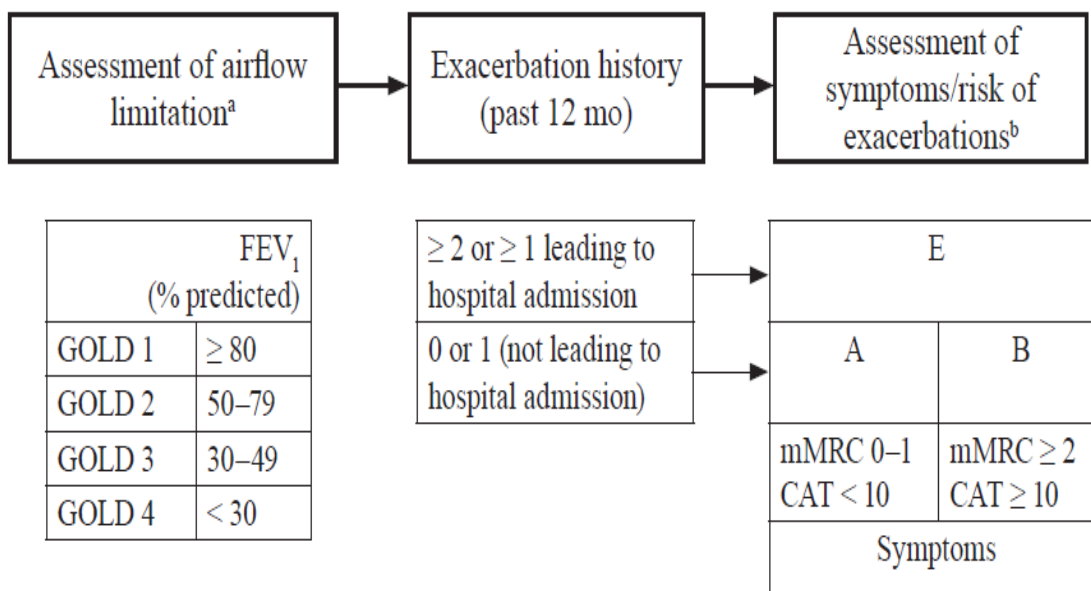
1-**Bronchodilators are the mainstay of drug therapy**; classes include short- and long-acting  **$\beta$ 2-agonists**, short- and long-acting **muscarinic antagonists** (anticholinergics), and **methylxanthines**.

2-Short-acting inhaled bronchodilators **relieve symptoms** (e.g., dyspnea). Long acting inhaled bronchodilators **relieve symptoms and reduce exacerbation frequency**.

### **Patient assessment and selection of therapy**

GOLD guidelines combine **symptoms** (by **questionnaires**) and **frequency of exacerbations** in the previous 12 months to determine patient risk group **and recommend initial treatment** (Figure 1 and 2) <sup>(2)</sup>.

Note



<sup>a</sup>Post-bronchodilator FEV<sub>1</sub> should be used.

<sup>b</sup>CAT score is preferred, but any can be used.

CAT = COPD Assessment Test (validated questionnaire); GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = Modified Medical Research Council breathlessness scale (validated questionnaire).

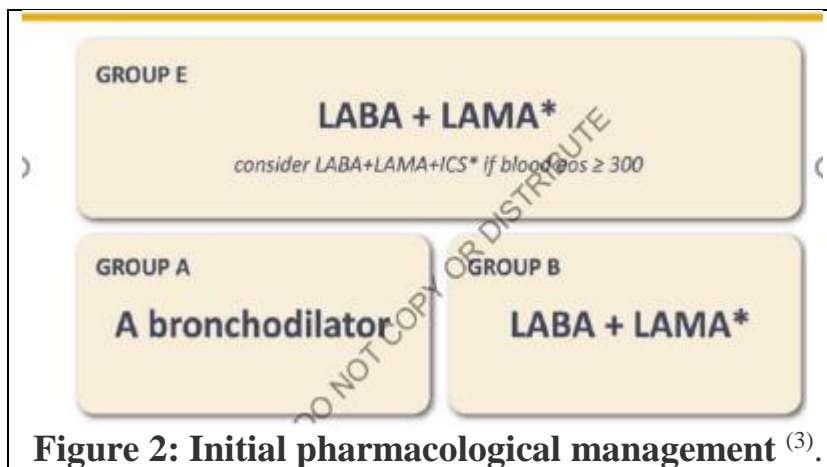
**Figure 1. GOLD guidelines: refined assessment of COPD severity and risk** <sup>(2)</sup>.

## Initial pharmacological management

1-Rescue short-acting bronchodilators should be prescribed to all patients for immediate symptom relief <sup>(3)</sup>.

2-Group A: All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be **either a short- or a long-acting bronchodilator** <sup>(3)</sup>.

3-Group B: Treatment should be initiated with a **LABA+LAMA combination**.



**Figure 2: Initial pharmacological management** <sup>(3)</sup>.

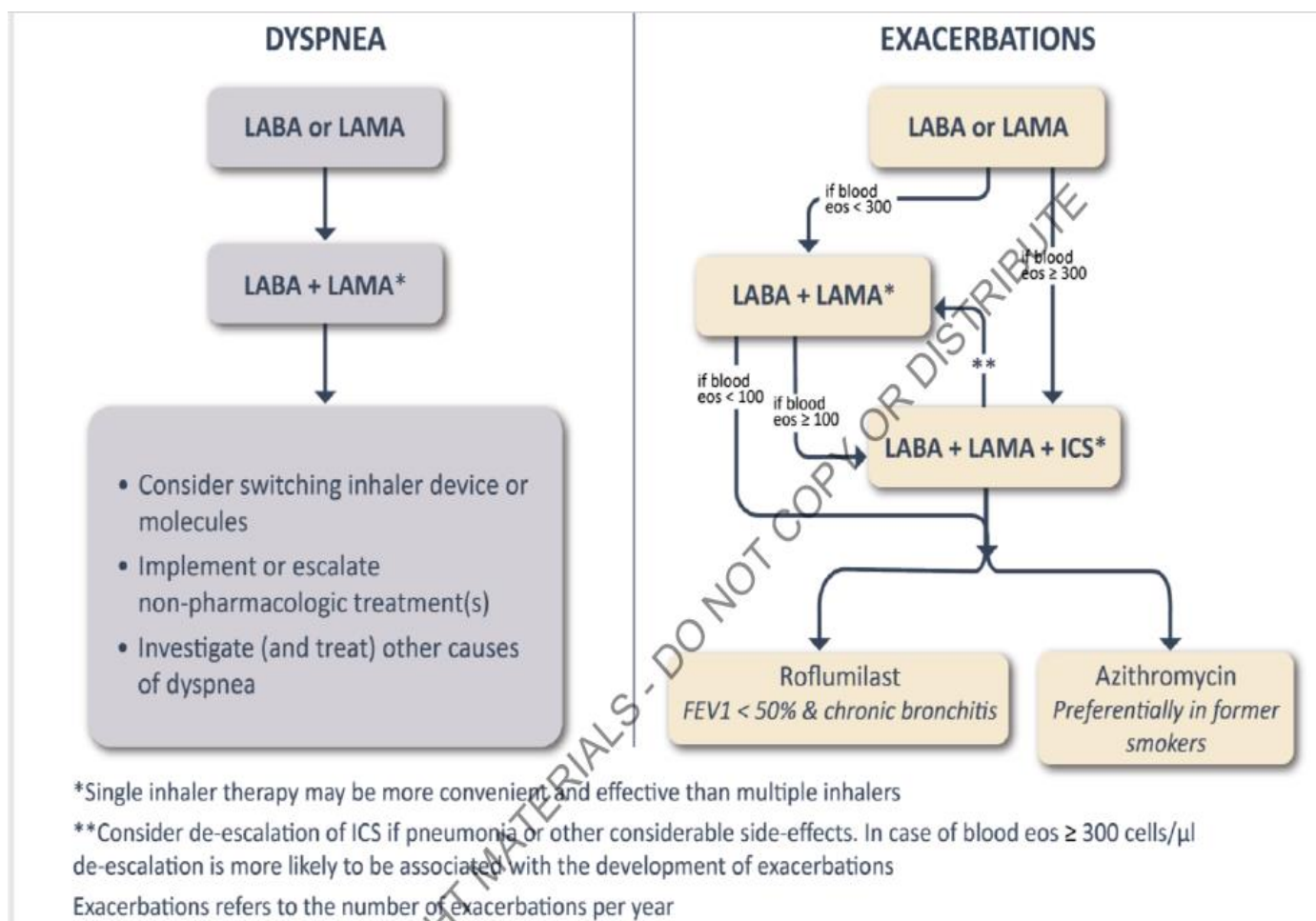
4-Group E (“E” for “Exacerbations”):

A-LABA+LAMA is the preferred choice for initial therapy in group E patients.

B-Consider LABA+LAMA+ICS in group E if eosinophil count ≥ 300 cells/μL.

## Maintenance therapy

Maintenance therapy adjustments are recommended according to the **predominant treatable trait** of **dyspnea** (Figure 3 left column); or **exacerbations** (Figure 3 right column). If **both exacerbations and dyspnea need to be targeted**, the **exacerbation pathway** should be followed <sup>(2, 3)</sup>.



**Figure 3: Maintenance therapy of COPD <sup>(3)</sup>.**

### **Dyspnea (patients with persistent dyspnea)**

For patients with persistent breathlessness or exercise limitation on bronchodilator monotherapy, **the use of two long acting bronchodilators is recommended <sup>(3)</sup>.**

### **Exacerbations [patients continuing to have exacerbations (with or without persistent dyspnea)]**

1-For patients with persistent exacerbations on bronchodilator monotherapy:

A-Escalation to **LABA+LAMA+ICS** may be considered **if blood eosinophil count ≥ 300 cells/ $\mu$ L<sup>(3)</sup>.**

B-If blood eosinophil count < 300 cells/ $\mu$ L escalation to **LABA+LAMA** is recommended <sup>(3)</sup>.

2-In patients on LABA+LAMA and still have exacerbations, Escalation to LABA+LAMA+ICS if eosinophil counts ≥ 100 cells/ml may be considered <sup>(3)</sup>.

3-In patients on LABA+LAMA and eosinophil counts < 100 cells/ $\mu$ L who still have exacerbations, or patient treated with LABA+LAMA+ICS and still have exacerbations, the following options may be considered <sup>(3)</sup>:

**A-Add roflumilast.** This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis <sup>(3)</sup>.

**B-Add azithromycin** (especially in those who are not current smokers) <sup>(3)</sup>.

## Short-Acting Bronchodilators

1-**Either a short- or long-acting bronchodilator** is recommended initially for patients with occasional symptoms (**category A**).

2-Short acting bronchodilators are also recommended **for all patients (categories A–E) as rescue or as-needed therapy to manage symptoms.**

3-Choices among short-acting bronchodilators include **short-acting  $\beta$ 2-agonists (SABAs)** or **short-acting muscarinic antagonists (SAMAs)**. Both drug classes have a relatively rapid onset of action, **relieve symptoms** to a similar degree, and **improve exercise tolerance** and lung function.

4-Short-acting bronchodilators **do not reduce the frequency or severity of COPD exacerbations.**

5-If a patient does not achieve adequate symptom control with one agent, **combining a SABA with a SAMA is reasonable.**

6-The SABA choices include albuterol and levalbuterol. **Inhalation** is the preferred route for SABAs, and administration via metered-dose or dry powder inhalers (**MDIs, DPIs**) is at least as effective as nebulization therapy and is more convenient and less costly.

7-**Inhaled SABAs are generally well tolerated; they can cause** sinus tachycardia and rhythm disturbances rarely in predisposed patients. **Skeletal muscle tremors** can occur initially but generally subside as tolerance develops. Older patients may be more sensitive and experience palpitations, tremors, and “jittery” feelings.

8-**Ipratropium bromide** is the most commonly prescribed SAMA. Improvements in pulmonary function are similar to inhaled SABAs, **although ipratropium has a slower onset of action (15–20 minutes vs. 5 minutes for albuterol) and more prolonged effect.**

9-Because of its slower onset, **ipratropium may be less suitable for as needed use but is often prescribed in this manner.**

10-The most frequent **patient complaints** are dry mouth, nausea, and occasionally metallic taste.

## Long-Acting Bronchodilators

1-Therapy can be administered as an inhaled **long-acting  $\beta$ 2-agonist (LABA)** or **muscarinic antagonist (LAMA)**. There is no dose titration for any of these agents; the starting dose is the effective and recommended dose for all patients.

2-The available LABA **formoterol**, has an onset of action similar to albuterol (<5 minutes), whereas **salmeterol** has a slower onset (15–20 minutes); **however, none of these agents are recommended for acute relief of COPD symptoms.**

5-The available LAMA: **tiotropium** has an onset of action (80 minutes) and is not recommended for acute relief of symptoms.

## **Methylxanthines (Theophylline and aminophylline)**

1-Methylxanthines have a limited role in COPD therapy because of the availability of LABAs and LAMAs as well as **significant methylxanthine drug interactions and interpatient variability in dosage requirements.**

2-Theophylline may be considered in patients **intolerant of or unable to use inhaled bronchodilators.**

3-**Sustained-release theophylline preparations** are most appropriate for long-term COPD management. Caution should be used in **switching from one sustained-release preparation to another** because of variability in sustained-release characteristics.

4-**Common theophylline side effects** include dyspepsia, nausea, vomiting, diarrhea, headache, dizziness, and tachycardia. Arrhythmias and seizures may occur, especially at toxic concentrations.

## **Corticosteroids**

1-The clinical benefits of ICS therapy **have been observed with combination therapy. ICS monotherapy is not recommended for patients with COPD.**

2-Short-term systemic corticosteroids may **also be considered for acute exacerbations. Chronic systemic corticosteroids should be avoided in COPD** because of questionable benefits and high risk of toxicity.

## **Roflumilast**

1-Roflumilast is a **phosphodiesterase 4 (PDE4) inhibitor** that relaxes airway smooth muscle.

2-Roflumilast is recommended for patients with recurrent exacerbations **despite treatment with triple inhalation therapy (LAMA/LABA/ICS) or [dual therapy (LAMA/LABA) who are not candidates for ICS (eosinophil count <100 cells/  $\mu$ L)].**

3-Because theophylline and roflumilast have similar mechanisms of action, **they should not be used together.**

## **Azithromycin**

1-Chronic **azithromycin was associated with a lower rate of COPD exacerbation** but also with colonization with macrolide resistant bacteria and hearing deficits.

2-In addition, the azithromycin product labeling includes **a precaution about QT prolongation.**

3-Current guidelines recommend to consider **adding chronic azithromycin only for patients with recurrent exacerbations despite optimal therapy (especially in those who are not current smokers)** <sup>(3)</sup>.

## **COPD exacerbations**

1-A COPD exacerbation is defined as **a change in the patient's baseline symptoms (dyspnea, cough, or sputum production)** (worsening dyspnea, increased sputum volume, or increased sputum purulence) **sufficient to warrant a change in management.**

## 2- Classification <sup>(2)</sup>:

- A. Mild: SA bronchodilators only
- B. Moderate: SA bronchodilators plus antibiotics and/or oral corticosteroids
- C. Severe: hospitalization or emergency department (ED) visits

**3-Goals of Treatment:** (1) Minimize the negative consequences of the acute exacerbation (i.e., reduce symptoms, prevent hospitalization, shorten hospital stay, prevent acute respiratory failure or death) and (2) prevent future exacerbations.

## Nonpharmacologic therapy

**1-Provide oxygen therapy for patients with significant hypoxemia.**

**2-Noninvasive positive-pressure ventilation (NPPV)** provides ventilatory support with oxygen using a face or nasal mask **without endotracheal intubation.**

**3-Intubation and mechanical ventilation** may be needed in patients failing NPPV or who are poor candidates for NPPV.

## Pharmacologic Therapy

The three classes of medications most commonly used for COPD exacerbations are bronchodilators, corticosteroids, and antibiotics <sup>(3)</sup>.

### A-Bronchodilators

1-It is recommended that inhaled SABAs are the initial bronchodilators for acute treatment of a COPD exacerbation <sup>(3)</sup>. **SABAs are preferred** because of rapid onset of action. **Muscarinic antagonists may be added** if symptoms persist despite increased doses of  $\beta$ 2-agonists.

2-Bronchodilators may be administered via **MDI, DPI, or nebulization** with equal efficacy. **Nebulization** may be considered for patients with severe dyspnea **who are unable to hold their breath after actuation of an MDI.**

3-Methylxanthines are not recommended due to increased side effect profiles. [**I.V methylxanthines (theophylline or aminophylline) are not recommended due to significant side effects**] <sup>(3)</sup>.

### B-Corticosteroids

Although the optimal corticosteroid dose and duration are unknown, **prednisone 40 mg orally daily (or equivalent) for 5 days is effective for many patients.**

### C-Antimicrobial Therapy

1-In order to limit unnecessary use, antibiotics should be initiated in any of these clinical situations:

- (1) patients presenting **with three cardinal symptoms** of acute exacerbation (worsening dyspnea, increased sputum volume, or increased sputum purulence).
- (2) patients presenting with **two cardinal symptoms** as long as one is **increased sputum purulence.**
- (3) patients requiring **mechanical ventilation** regardless of symptoms.

2-The most common pathogens in COPD exacerbations are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* <sup>(2)</sup>.

3-The choice of the antibiotic should be **based on the local bacterial resistance pattern**. Usually, initial empirical treatment is **an aminopenicillin with clavulanic acid, macrolide, tetracycline** or, in selected patients, **quinolone** <sup>(3)</sup>.

3-**Continue antimicrobial therapy for at least 5–7 days**. If the patient deteriorates or does not improve as anticipated, hospitalization may be necessary, and more aggressive attempts should be made to identify potential pathogens responsible for the exacerbation.

### **Evaluation of therapeutic outcomes**

1-**In chronic stable COPD, assess pulmonary function tests annually** and with any treatment additions or discontinuations.

2-**In acute exacerbations of COPD**, assess white blood cell count, vital signs, chest x-ray, and changes in frequency of dyspnea, sputum volume, and sputum purulence at the onset and throughout treatment of the exacerbation.

3-**In more severe exacerbations**, ABG and SaO<sub>2</sub> should also be monitored.

### **Reference**

1-Joseph T. DiPiro, Robert L. Pharmacotherapy: A Pathophysiologic Approach, 12<sup>th</sup> Edition. 2023.

2-ACCP 2023

3-Global Initiative for Chronic Obstructive Lung Disease. GLOBAL STRATEGY FOR PREVENTION, DIAGNOSIS AND MANAGEMENT OF COPD: 2023 Report. Global Initiative for Chronic Obstructive Lung Disease - GOLD. 2023.

### **Further reading**

Pharmacological and non-pharmacological therapies with evidence of efficacy in reducing the mortality of COPD patients include [Triple combinations (LABA+LAMA+ICS), Smoking cessation, Pulmonary rehabilitation, Long term oxygen therapy, Non-invasive positive pressure ventilation, Lung transplantation and lung volume reduction surgery] <sup>(3)</sup>.